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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/421,422	10/19/1999	PEHR B. HARBURY	8600-0197.30	4130
22918	7590	05/20/2004	EXAMINER	
PERKINS COIE LLP			TRAN, MY CHAU T	
P.O. BOX 2168			ART UNIT	
MENLO PARK, CA 94026			PAPER NUMBER	

1639

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/421,422	Applicant(s) HARBURY ET AL.	
	Examiner MY-CHAU T TRAN	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 19 October 0199 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Note: The examiner for your application in the PTO has changed. However, the Group and/or Art Unit location of your application in the PTO is remained the same, which is Group Art Unit 1639.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/20/04 has been entered.

Status of Claims

2. Claims 1-14 are pending.
3. This application claims priority to a provisional application 60/104,744 filed 10/19/98.
4. Claims 11-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7 (dated 3/26/01).
5. Claims 1-10 are treated on the merit in this Office Action.

Withdrawn Rejections

6. The previous rejection under 35 USC 112, first paragraph (enablement) has been withdrawn in view of new ground of rejection.
7. The previous rejections under 35 USC 112, second paragraph, have been withdrawn in view of new ground of rejections.

New Rejections

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (This is a written description rejection)

The instant claim 1 recites a method of tag-directed synthesis of a plurality of compounds. The method comprises the steps of a) forming a first group of subsets of nucleic acid tags, b) reacting the chemical reaction sites in each of the subsets formed in (a) with a first selected reagent to form a reagent-specific compound intermediate, c) forming a second group of subsets of the reacted-nucleic acid tags, and d) reacting the compound intermediates in each of the subsets formed in (c) with a second reagent, whereby the nucleic acid tags direct the

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synthesis of the compounds. The nucleic acid tags of the first group of subsets comprise a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site. The nucleic acid tags of the second group of subsets comprise a plurality of different second hybridization sequences, and a mixture of different first hybridization sequences.

The specification disclosure does not sufficiently teach the claimed method of tag-directed synthesis using “nucleic acid tag” for synthesizing *any* compounds. The specification description is directed to a method of synthesizing DNA library specifically base-specific duplex formation using “nucleic acid tag” (pg. 12, lines 5-8; pg. 14, line 9 to pg. 15, line 22). Thus the specification does not teach the claimed method of tag-directed synthesis using “nucleic acid tag” for synthesizing *any* compounds such as peptides, oligosaccharides, or antibody.

The specification disclosure does not sufficiently teach the claimed method of tag-directed synthesis wherein the nucleic acid tags of the first group of subsets comprise a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site, and the nucleic acid tags of the second group of subsets comprise a plurality of different second hybridization sequences, and a mixture of different first hybridization sequences. The specification description discloses *one* group of subsets of nucleic acid tags (pg. 11, lines 24-29; pg. 12, line 22 to pg. 13, line 21; pg. 14, lines 29-32). The specification specifically discloses that “*each tag has a first segment* having a selected one of a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site; *and a second segment* having a selected one of a plurality of different second hybridization sequences and a mixture of different first

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hybridization sequences” (pg. 11, lines 24-29). Therefore, the specification does not teach the claimed method of tag-directed synthesis wherein the nucleic acid tags of the first group of subsets comprise a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site, and the nucleic acid tags of the second group of subsets comprise a plurality of different second hybridization sequences, and a mixture of different first hybridization sequences.

The specification disclosure does not sufficiently teach the claimed method of tag-directed synthesis wherein the method comprises the steps of forming a second group of subsets of the reacted-nucleic acid tags, and reacting the compound intermediates in each of the second group of subsets formed with a second reagent. The specification description is directed to forming *one* group of subsets of nucleic acid tags (pg. 11, lines 24-29; pg. 12, line 22 to pg. 13, line 21; pg. 14, lines 29-32). The specification is silent on the method steps of forming a second group of subsets of the reacted-nucleic acid tags, and reacting the compound intermediates in each of the second group of subsets formed with a second reagent.

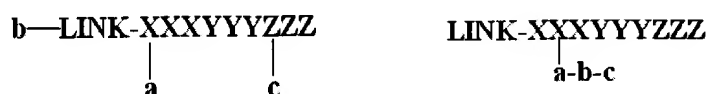
The specification disclosure does not sufficiently teach the claimed method of tag-directed synthesis wherein the method step of attaching a reagent to the “nucleic acid “ tag encompasses *any* type of reaction mechanisms. For example, the “nucleic acid “ tag comprises LINK-XXXYYYZZZ, wherein LINK denotes either a solid support with a functional group (chemical reaction site) or a chemical linker with a functional group (chemical reaction site), and ‘X’, ‘Y’, and ‘Z’ denotes nucleic acid that comprises several different “chemical reaction site” such as nucleotide base, sugar, or the backbone. Thus there is several different mode of

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attaching the reagent to the "nucleic acid" tag. Some examples of the reaction mechanisms for attaching reagents are as follows: (reagents are denoted as 'a', 'b', and 'c')

➤ d-c-b-a- LINK-XXXYYYYZZZ;

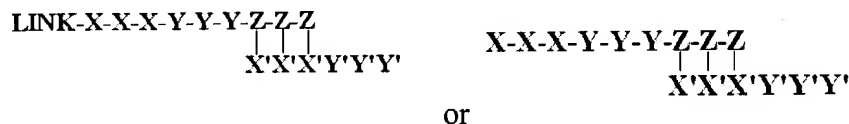
➤ LINK-XXXYYYYZZZ-a-b-c-d;



➤ Branching such as: or

➤ Extending the length of the 'nucleic acid' tag such as:

LINK-XXXYYYYZZZX'X'X'Y'Y'Y'; or by hybridization such as



In each of these reaction mechanisms the chemistry required for attachments of the reagent(s) is constrained by the type of protecting group use and the method of deprotection. The specification description is directed to a method of synthesizing DNA library specifically base-specific duplex formation using "nucleic acid tag" (pg. 12, lines 5-8; pg. 14, line 9 to pg. 15, line 22). Thus the specification does not teach the claimed method of tag-directed synthesis wherein the method step of attaching a reagent to the "nucleic acid" tag encompasses *any* type of reaction mechanisms other than hybridization to form base-specific duplex.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See Vas-Cath at page 1117.) The specification does not "clearly

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allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."

(See Vas-Cath at page 1116.).

With the exception of the method of synthesizing DNA library specifically base-specific duplex formation using "nucleic acid tag" disclosed by the specification, the skilled artisan cannot envision the claimed method of tag-directed synthesis wherein the method would a) synthesize *any* compounds, b) encompasses *any* type of reaction mechanisms c) comprise the steps of forming a second group of subsets of the reacted-nucleic acid tags, and reacting the compound intermediates in each of the second group of subsets formed with a second reagent, and d) forming two groups of nucleic acid tags. Adequate written description requires more than a mere statement that it is part of the invention and/or reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

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In the present instance, the specification supports the method of synthesizing DNA library specifically base-specific duplex formation using "nucleic acid tag". The specification does not teach the claimed method of tag-directed synthesis wherein the method would a) synthesize *any* compounds, b) encompasses *any* type of reaction mechanisms c) comprise the steps of forming a second group of subsets of the reacted-nucleic acid tags, and reacting the compound intermediates in each of the second group of subsets formed with a second reagent, and d) forming two groups of nucleic acid tags. Therefore, only the method of synthesizing DNA library specifically base-specific duplex formation using "nucleic acid tag", but not the full breadth of the claimed method of tag-directed synthesis wherein the method would a) synthesize *any* compounds, b) encompasses *any* type of reaction mechanisms c) comprise the steps of forming a second group of subsets of the reacted-nucleic acid tags, and reacting the compound intermediates in each of the second group of subsets formed with a second reagent, and d) forming two groups of nucleic acid tags meet the written description provision of 35 U.S.C 112, first paragraph.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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a. Claim 1 recites “a chemical reaction site in each of the subsets of the nucleic acid tags” is indefinite because it is unclear to the means of determining the “location” of the reaction site on the “nucleic acid tag” (i.e. where on the tag is the reagent being attached).

b. The recitation of “the reacted-nucleic acid tags” of claim 1 is vague and indefinite because it is unclear if it is referring to the “reagent-specific compound intermediate formed in step (b) or the ‘product’ of the claimed method. Furthermore, step (d) refers to “the reacted-nucleic acid tags” as the ‘compound intermediates’.

c. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are:

- 1) The step between step (b) forming the ‘reagent-specific compound intermediate’ and step (c) forming the second group of tags because it is unclear as to the correlation between these to step (i.e. what happen to the ‘reagent-specific compound intermediate’).
- 2) The step between step (b) forming the ‘reagent-specific compound intermediate’ and step (d) forming the compounds of the claimed method because it is unclear as to the “role” in which the ‘reagent-specific compound intermediate’ play in forming the compounds of the claimed method since the combination of method steps (c) and (d) would produce the “compounds” where as the combination of method steps (a) and (b) would produce the “compound intermediate”.

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- d. The term 'reagents' of claim 2, line 4 is indefinite because it is unclear whether this reagent refers to the "solid phase reagent" of the surface bound oligonucleotide or the reagents of claim 1 in step (b) and/or (c).
- e. Claim 5 recites the limitation "synthetic step" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim 1.
- f. The recitation of "a selected subunit" of claim 3 and "a selected chemical substituent" of claim 4 are vague and indefinite because it is unclear if the "subunit" and "chemical substituent" or are they referring to the reagents of claim 1 (i.e. first reagent and second reagent). Furthermore, it is unclear if there is a relationship (i.e. structural and/or functional) among these 'compounds' (i.e. "subunit", "chemical substituent", "first reagent" and "second reagent")

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an

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international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 1, and 3-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Brenner et al. (*Proc. Natl. Acad. Sci.*, **1992**, 89(12):5381-5383).

Brenner et al. disclose the method of two alternating parallel combinatorial syntheses wherein the genetic tag is chemically link to the chemical structure being synthesized (pg. 5381, right col., lines 47-54). In general, the method comprises the addition of monomeric chemical unit to a polymeric structure that is followed by the addition of an oligonucleotide sequence, which is defined a “encoding” that chemical unit (tag-directed synthesis). The library of compounds is built up by the repetition of this process after pooling and division. The method comprises the steps of 1) synthesizing the first PCR oligonucleotide sequence on one end of the solid support, 2) dividing the PCR oligonucleotide bound to a support into two aliquots for parallel synthesis, 3) adding to each aliquots an amino acid (first reagent/subunit) and an oligonucleotide coding sequence (chemical substituent) for the amino acid wherein the amino acid is attached to the other end of the solid support and the oligonucleotide coding sequence is attached to the PCR oligonucleotide, which would extend the PCR oligonucleotide sequence (refers to step (b) of claim 1 and claims 3-4), 4) the two aliquots are pooled and again split for parallel synthesis in which step (3) is repeated to form the desired elongated product (reagent-specific compound intermediate) (refers to claim 5), and 5) attaching the second PCR oligonucleotide to the elongated product to produce a library of compounds (pg. 5382, right col.,

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lines 34-66). The compound comprises a genetic tag, a solid support, and peptide sequences. The elongated product (first group) comprises a plurality of oligonucleotide coding sequences (a mixture of different second hybridization sequences), the first PCR oligonucleotide sequence (first hybridization sequence), and a solid support (chemical reactive site) wherein the amino acid is attached. Additionally, Brenner et al. disclose that DNA strands with the appropriate polarity can then be used to enrich for a subset of the library by hybridization with matching tags, and the process can then be repeated on this subset (refers to steps (c) and (d) of claim 1). Thus the method of Brenner et al. anticipates the presently claimed method.

14. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Brenner (US Patent 5,604,097).

Brenner discloses a method of sorting polynucleotides from a mixture of polynucleotides by hybridizing the polynucleotides to their complements of oligonucleotide tags (tag-directed synthesis) (col. 3, lines 33-58). Each of the polynucleotides (first group of subsets of nucleic acid tags) of a mixture of polynucleotides to be sorted comprises an oligonucleotide tag in the repertoire such that identical polynucleotides have the same tag and different polynucleotides have different tags (col. 3, lines 48-51). The oligonucleotide tags (second group of subsets of nucleic acid tags) comprise a repertoire of complements with distinct sequences wherein the size of the repertoire depends on the number of subunits and length of subunits employed (col. 3, lines 44-48). The method of synthesizing the polynucleotide of a mixture of polynucleotides comprises the steps of 1) an oligonucleotide segment (first hybridization sequence) is synthesized initially so that in double stranded form a restriction endonuclease site (adjacent

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spacer sequence) is provided for cleaving the library compound after sorting, and 2) adding alternating subunits to form the oligonucleotide tag (a mixture of different second hybridization sequences) and their corresponding compound monomers (reagent) via a "split and mix" technique (col. 12, lines 5-14) (refers to steps (a) and (b) of claim 1). The oligonucleotide tags are synthesized on a solid phase support by subunit-wise synthesis via "split and mix" technique (col. 3, lines 33-58; col. 8, lines 16-37) (refers to step (c) of claim 1). The oligonucleotide tag and the mixture of polynucleotide are reacted to form perfectly formed duplexes by hybridization (col. 16, lines 1-19) (refers to step (d) of claim 1 and claim 2). Additionally, the duplexes are identified by way of polynucleotide sequencing (col. 19, line 52 to col. 20, line 14). Therefore the method of Brenner anticipates the presently claimed method.

15. Claims 1, and 7-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Brenner (US Patent 5,962,228).

Brenner discloses a method of synthesizing polynucleotides from a mixture of polynucleotides by hybridizing the polynucleotides to their complements of oligonucleotide tags (tag-directed synthesis) (col. 3, lines 26-46). Each of the polynucleotides (first group of subsets of nucleic acid tags) of a mixture of polynucleotides to be sorted comprises an oligonucleotide tag in the repertoire such that identical polynucleotides have the same tag and different polynucleotides have different tags (col. 4, lines 45-59) (refers to steps (a) and (b) of claim 1). The oligonucleotide tags (second group of subsets of nucleic acid tags) comprise a repertoire of complements with distinct sequences wherein the size of the repertoire depends on the number of subunits and length of subunits employed (col. 4, lines 14-44). The oligonucleotide tags are

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synthesized on a solid phase support by subunit-wise synthesis via "split and mix" technique (col. 4, lines 45-59; col. 13, lines 7-13) (refers to step (c) of claim 1). Additionally, the duplexes are identified by way of polynucleotide sequencing (col. 17, line 27 to col. 20, line 59). Therefore the method of Brenner anticipates the presently claimed method.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MY-CHAU T TRAN whose telephone number is 571-272-0810. The examiner can normally be reached on Mon.: 8:00-2:30; Tues.-Thurs.: 7:30-5:00; Fri.: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANDREW WANG can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

mct

May 14, 2004


PADMASHRI PONNALURI
PRIMARY EXAMINER